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CASE REPORTS

An Atypical Case of Miller Fisher Syndrome with Multiple Autoimmunity

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ABSTRACT

Miller Fisher syndrome (MFS) is a rare variant of Guillain–Barré syndrome that is characterised by ataxia, ophthalmoplegia, and areflexia. Its relation with other autoimmune diseases is scarcely found in the literature, and in those few cases, treatment has been especially difficult. We report a case of a 28-year-old woman who presented with ophthalmoplegia and ptosis, later developing facial palsy and hyporeflexia. She had positive GD1a, GT1a, GQ1b antibodies confirming MFS. She also had positive antinuclear and lupus anticoagulant antibodies confirming antiphospholipid syndrome. She had a mild clinical course. MFS can present with multiple autoimmunity; it is unclear if there is cross-reactivity due to myelin damage.

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Introduction

Miller Fisher syndrome (MFS) is a rare variant of Guillain–Barré syndrome that is characterised by ataxia, ophthalmoplegia, and areflexia. Its relation with other autoimmune diseases is scarcely found in the literature, and in those few cases, treatment has been especially difficult. We report a case of a 28-year-old woman who presented with ophthalmoplegia and ptosis, later developing facial palsy and hyporeflexia.

Case report

A 28-year-old woman presented to the ophthalmology emergency room with a 6-day history of decreased visual acuity followed by double vision. She had a medical history of hypothyroidism treated with levothyroxine. She had a past ocular history of keratoconus. The family history was non-contributory.

On initial neurological examination, she had binocular diplopia, complete ophthalmoplegia bilaterally, and ptosis of the left eye. (Figure 1). She had a non-corrected visual acuity of 20/50 OU, which was considered to be not relevant due to her keratoconus history.

Seven days later she developed bilateral facial palsy that was worse on the left, tongue dysaesthesia, and bilateral non-reactive, 4.5-mm pupils (Figure 2). She was hyporeflexiac but did not have any ataxia. She was admitted to the hospital for further investigation.

Electromyography (EMG) revealed normal orbicularis and extensor digitorum function. Contrast-enhanced magnetic resonance imaging (MRI) of the brain revealed a retro-cerebellar arachnoid cyst without any compressive effect. Cerebrospinal fluid (CSF) analysis yielded a slightly increased protein level (48 mg/dl) but normal glucose concentration. CSF viral serology, gram stain, and culture were negative.

Non-treponemal and treponemal studies for syphilis were negative. Serum antibody testing, through immunoblotting for immunoglobulin G (IgG) antibodies to the ganglioside complex (GSC) was performed. GD1a, GT1a, and GQ1b antibodies were positive; IgG for GM1, GM2, GM3, GD1b, GT1b were negative. Additional laboratory workup revealed positive antinuclear (ANA) (1:320 dilution, granular pattern), lupus anticoagulant, anticardiolipin immunoglobulin M (3.0 UI/ml), anticardiolipin IgG (2.8 Ul/ml), and anti-beta2-glycoprotein I IgG (2.0 Ul/ml) antibodies.

A diagnosis of incomplete MFS was made with multiple autoimmune involvement. A rheumatology consultation was arranged and a diagnosis of antiphospholipid syndrome was made. Treatment with

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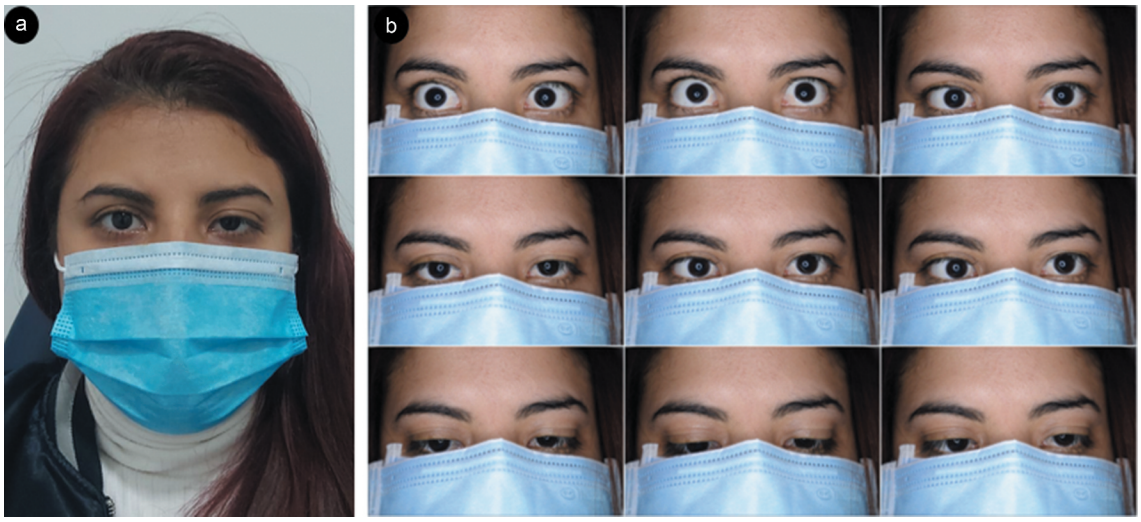

Figure 1. Primary gaze and nine-gaze photograph. The patient has (a) ptosis in the left eye and (b) complete external ophthalmoplegia in the nine-cardinal position of gaze at time of onset.

Figure 2. (a) Bilateral non-reactive, 4.5-mm pupils and (b) bilateral facial palsy with left-sided predominance.

oral prednisolone (30 mg initial dose), chloroquine (150 mg), and low molecular weight heparin (enoxaparin 40 mg) was started to treat the antiphospholipid syndrome.

After 2 weeks of treatment, improvement of ptosis was noted. She continued on chloroquine and was tapered down from prednisone. One month after onset, she started to improve gradually.

Discussion

MFS is a rare disorder characterised by ataxia, ophthalmoplegia, and areflexia. It is a variant of Guillain–Barré syndrome (GBS), accounting for 5% of its cases.[1] GBS is often preceded by a mild viral or bacterial infection, with respiratory or gastrointestinal illness. Neurological symptoms appear 8–10 days after and progress over the next 6 days.[2] It generally has a good prognosis, with improvement usually starting in the next month with supportive care and immunotherapy.[3]

Positivity for antiganglioside antibodies is common, but there is a small portion (<10%) who are seronegative.[1] There are different subtypes of GBS, and each can express different antiganglioside markers. GQ1b is present in oculomotor nerves and dorsal ganglia; this explains its correlation with different subtypes presenting with ophthalmoplegia and making this the most common finding in the MFS triad.[4,5] Our patient had anti-GQ1b, GT1a, and GD1b positivity, a profile that can be similar to that found in pharyngeal-cervical-brachial weakness (PCBW), another subtype of GBS.[6] Regardless, to make the diagnose of MFS, clinical and serological factors must be taken into account.

Our patient had various typical findings for MFS including bilateral ophthalmoplegia, hyporeflexia, antiganglioside positivity, and increased CSF protein. The typical CSF finding in GBS is albumin-cytological dissociation, which depends on the timing of the lumbar puncture.[2]

A study by Jung et al., evaluating atypical clinical manifestations of MFS, showed that 8% of their study population developed facial palsy sometime after the onset of neurological symptoms.[7] This happened after compromise of cranial nerves three, four, and six in all of the patients. This was consistent with our patient's presentation; she developed facial palsy 13 days after the onset of symptoms.

Tests such as MRI and EMG are ordered to rule out other diseases when the diagnosis is unclear, but they are often normal in MFS. An incidental finding in our patient was the presence of a retrocerebellar arachnoid cyst. Even though in some cases, these lesions can cause space-occupying symptoms such as gait disturbances similar to those seen in patients with MFS, this was not the case in our patient.

An interesting finding in our patient was the seropositivity for other antibodies, such as ANA and lupus anticoagulant antibodies. This is an infrequent presentation. A positive ANA has been found in only a few cases of MFS.[8–10] Only two cases of positive lupus anticoagulant with MFS have been previously reported in the literature.[11,12] It has been proposed that autoimmune reactivity contributes to MFS presentation.[13] Antiphospholipid syndrome has been rarely associated with GBS but can occur and must be suspected in cases of thrombosis and prolongation of common pathway factors. The most common subtype of antiphospholipid antibodies is IgM to anti-beta2-glycoprotein 1.[14–16] Some studies suggest that GBS patients produce autoantibodies to various phospholipid antigens as a result of myelin damage.[17]

MFS can be a self-limiting disease. In our case, steroid treatment was started for antiphospholipid syndrome but was not considered for MFS due to its mild clinical course. A broad spectrum of manifestations has been reported in the literature. Patients with MFS accompanied by other autoimmune diseases have generally had a severe course. The first case of MFS complicating systemic lupus erythematosus (SLE) mimicked a brainstem syndrome and did not respond to immunoglobulin treatment.[8] Another patient with known SLE and classic MFS was particularly refractory to treatment; intravenous immunoglobulin with corticosteroid pulse therapy was not enough to achieve improvement. Despite treatment, the disease progressed to tetraplegia and the patient required full mechanical ventilatory support, before subsequent successful treatment with plasma exchange.[9] In cases of paralysis due to GBS and concomitant antiphospholipid syndrome, a significant problem can be at increased risk of pulmonary embolism and deep venous thrombosis from hypercoagulability; this was not the case in our patient as she did not have generalised weakness.

Various neuropsychiatric syndromes may precede or occur in SLE. The American College of Rheumatology have described 19 central, peripheral, and autonomic syndromes as neuropsychiatric SLE (NPSLE). Although antiganglioside antibodies have shown to be positive in patients with NPSLE, GBS has been rarely associated with NPSLE.[10,18]

In conclusion, MFS associated with antiphospholipid syndrome is an infrequent presentation

of GBS. It is unknown if our patient presented with positive antibodies due to cross-reactivity related to myelin destruction, as described in GBS cases. Multiple autoimmunity in MFS does not always translate to more challenging therapeutic course.

Declaration of interest statement

The authors report no conflict of interest.

References

1. Dagklis IE, Papagiannopoulos S, Theodoridou V, Kazis D, Argyropoulou O, Bostantjopoulou S. Miller-Fisher syndrome: are Anti-GAD antibodies implicated in its pathophysiology? *Case Rep Neurol Med*. 2016;2016:3431849. doi:10.1155/2016/3431849.
2. Al Othman B, Raabe J, Kini A, Lee AG. Update: the Miller Fisher variants of Guillain-Barré syndrome. *Curr Opin Ophthalmol*. 2019;30(6):462–466. doi:10.1097/ICU.0000000000000611.
3. Truong J, Conley J, Ashurst J. Miller-Fisher syndrome: a case report and review of the literature. *Clin Pract Cases Emerg Med*. 2020;4(4):653–655. doi:10.5811/cpcem.2020.7.48507.
4. Chiba A, Kusunoki S, Obata H, Machinami R, Kanazawa I. Serum anti-GQ1b IgG antibody is associated with ophthalmoplegia in Miller Fisher syndrome and Guillain-Barré syndrome: clinical and immunohistochemical studies. *Neurology*. 1993;43(10):1911–1917. doi:10.1212/WNL.43.10.1911.
5. Liu JX, Willison HJ, Pedrosa-Domellöf F. Immunolocalization of GQ1b and related gangliosides in human extraocular neuromuscular junctions and muscle spindles. *Invest Ophthalmol Vis Sci*. 2009;50(7):3226–3232. doi:10.1167/iovs.08-3333.
6. Teener JW. Miller Fisher's syndrome. *Semin Neurol*. 2012;32(5):512–516. doi:10.1055/s-0033-1334470.
7. Jung JH, Oh EH, Shin JH, et al. Atypical clinical manifestations of Miller Fisher syndrome. *Neurol Sci*. 2019;40(1):67–73. doi:10.1007/s10072-018-3580-2.
8. Hess DC, Awad E, Posas H, Sethi KD, Adams RJ. Miller Fisher syndrome in systemic lupus erythematosus. *J Rheumatol*. 1990;17:1520–1522.
9. Bingisser R, Speich R, Fontana A, Gmür J, Vogel B, Landis T. Lupus erythematosus and Miller-Fisher syndrome. *Arch Neurol*. 1994;51(8):828–830. doi:10.1001/archneur.1994.00540200108024.
10. Okoh HC, Lubana SS, Langevin S, Sanelli-Russo S, Abrudescu AA. Case of systemic lupus erythematosus presenting as Guillain-Barré syndrome. *Case Rep Rheumatol*. 2015;2015:528026. doi:10.1155/2015/528026.
11. Arimura H. Atypical Miller Fisher syndrome associated with antiphospholipid antibodies. *Rinsho shinkeigaku = Clinical neurology*. 2000;40(1):62; discussion 63.
12. Ishida S, Ura M, Kameoka K, Furukawa K, Tagami M. A case of atypical Miller Fisher syndrome associated with antiphospholipid antibodies. *Rinsho shinkeigaku = Clinical neurology*. 1999;39(4):448–451.
13. Mitoma H, Adhikari K, Aeschlimann D, et al. Consensus paper: neuroimmune mechanisms of cerebellar ataxias. *Cerebellum*. 2016;15(2):213–232. doi:10.1007/s12311-015-0664-x.
14. Englert H, Derue G, Hughes GR. Neurology and the lupus anticoagulant. *Eur Neurol*. 1985;24(6):422–425. doi:10.1159/000115836.
15. Sahebari M, Rastin M, Boostani R, Forughipour M, Hashemzadeh K, Sadeghi SH. Subtypes of antiphospholipid antibodies in neurologic disorders: an observational study. *Curr Rheumatol Rev*. 2019;15(1):59–66. doi:10.2174/1573397114666180514125412.
16. Harris EN, Englert H, Derve G, Hughes GR, Gharavi A. Antiphospholipid antibodies in acute Guillain-Barré syndrome. *Lancet*. 1983;2(8363):1361–1362. doi:10.1016/S0140-6736(83)91113-3.
17. Gilburd B, Stein M, Tomer Y, et al. Autoantibodies to phospholipids and brain extract in patients with the Guillain-Barre syndrome: cross-reactive or pathogenic? *Autoimmunity*. 1993;16(1):23–27. doi:10.3109/08916939309010644.
18. Labrador-Horrillo M, Martinez-Valle F, Gallardo E, Rojas-Garcia R, Ordi-Ros J, Vilardell M. Anti-ganglioside antibodies in patients with systemic lupus erythematosus and neurological manifestations. *Lupus*. 2012;21(6):611–615. doi:10.1177/0961203312436856.